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EP04/9819



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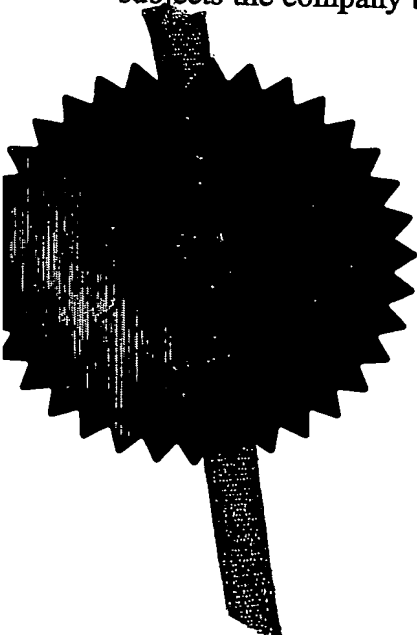
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Signed

*Stephen Handley*

Dated

24 August 2004

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05SEP03 E835103-1 D02029  
POL/7700 0.00-0320738.8

**1/77**

**Request for grant of a patent**

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The Patent Office

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1. Your Reference	ARG/PB60476P		
2. Patent application number (The Patent office will fill in this part)	04 SEP 2003 0320738.8		
3. Full name, address and postcode of the or of each applicant (underline all surnames)	GLAXO GROUP LIMITED GLAXO WELLCOME HOUSE BERKELEY AVENUE GREENFORD MIDDLESEX UB6 ONN GB		
00473587003 Patents ADP number (if you know it)			
If the applicant is a corporate body, give the country/state of its corporation	GB		
4. Title of the invention	NOVEL PROCESS		
5. Name of your agent (if you know one)	AMANDA R. GLADWIN		
"Address for service" in the United Kingdom to which all correspondence should be sent (including the postcode)	GLAXOSMITHKLINE CORPORATE INTELLECTUAL PROPERTY 980 GREAT WEST ROAD BRENTFORD, MIDDLESEX TW8 9GS, GB		
Patents ADP number (if you know it)	08072555005		
6. If you are declaring priority from one or more earlier patent applications, give the country and date of filing of the or of each of these earlier applications and (if you know it) the or each application number	Country	Priority application number (if you know it)	Date of Filing (day / month / year)
7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application		Date of filing (day / month / year)
8. Is a statement of inventorship and of right to grant a patent required in support of this request? (Answer yes if: a) any applicant named in part 3 is not an inventor, or b) there is an inventor who is not named as an applicant, or c) any named applicant is a corporate body.	YES		
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**Patents Form 1/77**

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Description	07
Claim(s)	02
Abstract	-
Drawing(s)	-



10. If you are also filing any of the following,  
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Priority Documents

Translations of priority documents

Statement of inventorship and right  
to grant of a patent (*Patents Form 7/77*)

Request for preliminary examination  
and search (*Patent Form 9/77*)

Request for substantive examination  
(*Patent Form 10/77*)

Any other documents  
(*please specify*)

11. I/We request the grant of a patent on the basis of this application

  
Signature **AMANDA R. GLADWIN 3 SEPTEMBER 2003**  
**AGENT FOR THE APPLICANTS**

12. Name and daytime telephone number of  
person to contact in the United Kingdom **SUE MORTON**  
**01438 76 8612**

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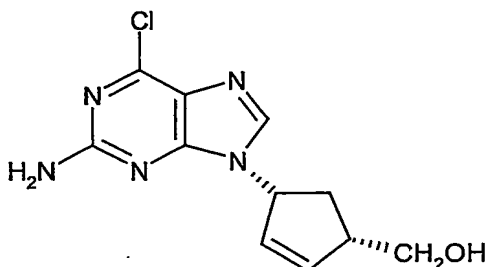
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## NOVEL PROCESS

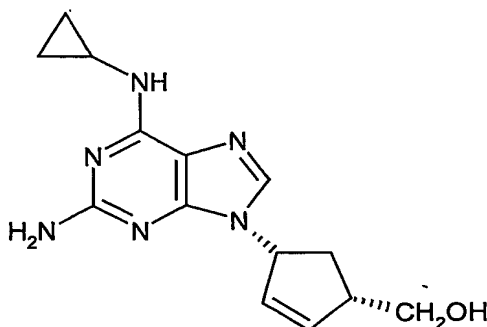
The present invention relates to a novel process for the preparation of a chloropurine compound of formula (I) or a pharmaceutically acceptable derivative thereof.

(1*S*,4*R*)-*cis*-4-[2-Amino-6-chloro-9*H*-purin-9-yl]-2-cyclopentene-1-methanol, the chloropurine compound of formula (I)



(I)

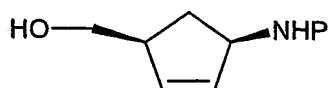
is described in European Patent No. 0 325 460 and can be used as an intermediate in the manufacture of abacavir ((1*S*,4*R*)-*cis*-4-[2-amino-6-(cyclopropylamino)-9*H*-purin-9-yl]-2-cyclopentene-1-methanol), a 2-aminopurine nucleoside compound of formula (II)



(II)

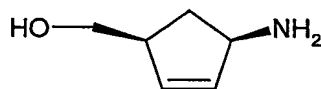
The antiviral use of abacavir, particularly in the treatment of the human immunodeficiency virus (HIV), is described in European Patent No. 0 434 450 and the hemisulfate salt of abacavir, described in International Patent Application No. WO98/52949, is commercially available from GlaxoSmithKline for the treatment of HIV under the tradename ZIAGEN®.

Processes for preparing abacavir and intermediates useful in the synthesis of abacavir have been described by, for example, Daluge *et al.* in Nucleosides, Nucleotides & Nucleic Acids, 19 (1&2), 2000, 297-327. International Patent Application No. WO99/19327 describes an *in situ* process for the preparation of the chloropurine compound of formula (I) which comprises hydrolysing a compound of formula (III)



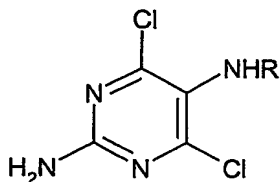
(III)

- 5 wherein P is a protecting group, in the presence of an acid, condensing the product of formula (IV) formed



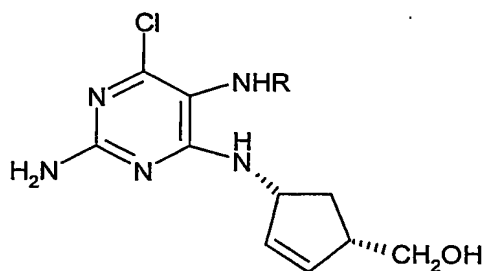
(IV)

- 10 *in situ* in the presence of a base with a compound of formula (V)



(V)

- 15 in which R represents CHO or H, followed by ring closure *in situ* of the resulting intermediate of formula (VI)



(VI)

20

According to WO99/19327, the ring closure reaction is preferably carried out in the presence of from about 1.5 to 3 molar equivalents of hydrochloric acid and a large excess of triethylorthoformate, which results in precipitation of the hydrochloride salt of the chloropurine compound of formula (I).

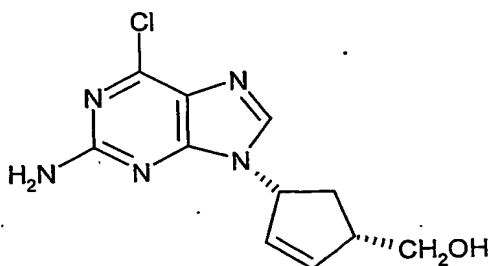
25

As abacavir is sold as a prescription medicine for the treatment of HIV infections, there exists a need to develop more efficient processes for preparing the compound in large quantities.

We have now found a process for preparing the chloropurine compound of formula (I) or a pharmaceutically acceptable derivative thereof in which the amount of both the

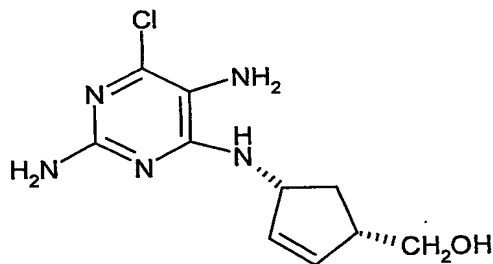
acid and formate derivative used in the cyclisation step is significantly reduced. The process according to the present invention thus allows abacavir and pharmaceutically acceptable derivatives thereof to be prepared without isolation of the highly toxic hydrochloride salt of the chloropurine compound of formula (I), which can be difficult to filter, and avoids the problems associated with handling gaseous hydrogen chloride. As a result, the process according to the present invention is a safer process in which the amount of solvent used is lowered, minimising waste and environmental impact, the cycle time is reduced, and the throughput and overall yield of the process is increased.

Accordingly, the present invention provides a process for preparing a chloropurine compound of formula (I)



(I)

or a pharmaceutically acceptable derivative thereof, which comprises ring closure of the compound of formula (VII) or a pharmaceutically acceptable derivative thereof



(VII)

in the presence of catalytic acid and at least one equivalent of a formate derivative.

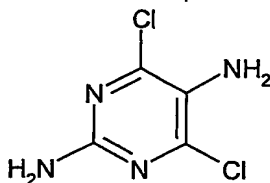
Acids suitable for use in the process of the present invention include concentrated aqueous and anhydrous mineral acids, for example sulfuric acid, hydrochloric acid, or an alkyl or arylsulfonic acid. Preferably, the acid is sulfuric acid. In order to effect ring closure, the acid is present in a catalytic amount. Typically, the acid is present in an amount of up to 0.1 equivalents by mole based on the amount of the compound of formula (VII), preferably from 0.01 to 0.05 equivalents.

Formate derivatives suitable for use in the process of the present invention include trialkylorthoformates such as trimethylorthoformate or triethylorthoformate, and diethoxymethyl acetate. Preferably, the formate derivative is triethylorthoformate. In the process of the present invention, the formate derivative is present in an amount of at least

one equivalent by mole based on the amount of the compound of formula (VII), preferably from 1 to 5 equivalents, more preferably from 1 to 2 equivalents and most preferably from 1 to 1.5 equivalents.

The ring closure reaction is preferably carried out in an anhydrous polar aprotic solvent, for example acetonitrile, anhydrous dimethylacetamide, dimethylformamide, or an alkanol solvent such as methanol, ethanol, n-butanol, iso-propanol (IPA) or industrial methylated spirit (IMS), in particular n-butanol. The reaction mixture is generally heated to a temperature of from 20 to 100°C, preferably from 40 to 80°C and more preferably from 60 to 70°C, for at least 3 hours.

The compound of formula (VII) may be prepared by condensing an amino alcohol of formula (IV) as hereinbefore defined or a pharmaceutically acceptable derivative thereof with a compound of formula (VIII) or a pharmaceutically acceptable derivative thereof



(VIII)

in the presence of a base.

The base is generally a trialkylamine such as triethylamine or an alkali metal carbonate or bicarbonate such as potassium or sodium carbonate or bicarbonate. Preferably, the base is an alkali metal bicarbonate such as potassium or sodium bicarbonate, in particular sodium bicarbonate. The base is present in an amount at least sufficient to neutralise the acid produced in the condensation reaction. Generally, there will be at least 2 equivalents by mole of base based on the amount of the compound of formula (IV), preferably from 2.2 to 5 equivalents.

The condensation reaction may be carried out under reflux in a polar solvent such as an alkanol, for example, methanol, ethanol, n-butanol, IPA or IMS, ethyl acetate or acetonitrile. Preferably, the condensation reaction is carried out in n-butanol. The reaction mixture is generally heated to a temperature of from 60 to 110°C, preferably from 80 to 110°C and more preferably from 90 to 100°C, for at least 8 hours.

In a preferred embodiment of the present invention, the condensation reaction is carried out in n-butanol in the presence of sodium bicarbonate. Preferably, once the condensation reaction is complete, the reaction mixture is diluted, filtered and then concentrated. Typically, the volume of solvent is reduced by at least 10%, preferably from 10 to 30%.

In a further preferred embodiment of the present invention, the condensation reaction is carried out in n-butanol in the presence of anhydrous potassium carbonate. The potassium carbonate removes the liberated water from solution thus avoiding the need for a concentration step.

The compound of formula (IV) may be prepared by the procedure described in WO99/19327 and the compound of formula (VIII) may be prepared by the procedure described in WO95/21161 and WO99/19327.

According to the process of the present invention, the ring closure reaction results in the formation of the chloropurine compound of formula (I) or a pharmaceutically acceptable derivative thereof. As the acid used in the ring closure reaction is only present in a catalytic amount, the chloropurine compound does not precipitate out as a salt but remains in solution. Thus, the chloropurine compound can be converted *in situ* to abacavir or a pharmaceutically acceptable derivative thereof.

When used herein, the term "pharmaceutically acceptable" means a derivative which is suitable for pharmaceutical use. Salts and solvates which are suitable for use in medicine are those wherein the counterion or associated solvent is pharmaceutically acceptable. However, salts and solvates having non-pharmaceutically acceptable counterions or associated solvents are within the scope of the present invention, for example, for use as intermediates in the preparation of other derivatives.

When used herein, the term "pharmaceutically acceptable derivative", means any pharmaceutically acceptable salt, solvate, or prodrug e.g. ester, which upon administration to the recipient is capable of providing (directly or indirectly) the compound, or an active metabolite or residue thereof. Such derivatives are recognizable to those skilled in the art, without undue experimentation. Nevertheless, reference is made to the teaching of Burger's Medicinal Chemistry and Drug Discovery, 5<sup>th</sup> Edition, Vol 1: Principles and Practice, which is incorporated herein by reference to the extent of teaching such derivatives. Preferred pharmaceutically acceptable derivatives are salts, solvates, esters, carbamates and phosphate esters. Particularly preferred pharmaceutically acceptable derivatives are salts, solvates and esters. Most preferred pharmaceutically acceptable derivatives are salts and esters, especially salts.

Compounds prepared using the process of the present invention may be in the form of and/or may be administered as a pharmaceutically acceptable salt. For a review on suitable salts see Berge *et al.*, J. Pharm. Sci., 1977, 66, 1-19.

Typically, a pharmaceutically acceptable salt may be readily prepared by using a desired acid or base as appropriate. The salt may precipitate from solution and be collected by filtration or may be recovered by evaporation of the solvent.

Salts prepared using the process of the present invention may, for example, comprise acid addition salts resulting from reaction of an acid with a basic nitrogen atom. Salts encompassed within the term "pharmaceutically acceptable salts" refer to non-toxic salts of the compounds of this invention. Suitable addition salts are formed from acids which form non-toxic salts and examples are acetate, p-aminobenzoate, ascorbate, aspartate, benzenesulfonate, benzoate, bicarbonate, bismethylenesalicylate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, cyclohexylsulfamate, dihydrochloride, edetate, edisylate, estolate, esylate, ethanedisulfonate, ethanesulfonate, formate, fumarate, gluceptate, gluconate, glutamate, glutarate, glycollate, glycollylarsanilate, hemisulfate, hexylresorcinate,



hydrabamine, hydrobromide, hydrochloride, hydrogen phosphate, hydroiodide, hydroxynaphthoate, iodide, isethionate, itaconate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, monopotassium maleate, mucate, napsylate, nitrate, N-methylglucamine, oxalate, oxaloacetate, pamoate (embonate), palmate, palmitate, pantothenate, phosphate/diphosphate, piruvate, polygalacturonate, propionate, saccharate, salicylate, stearate, subacetate, succinate, sulfate, tannate, tartrate, teoclate, tosylate, triethiodide, trifluoroacetate and valerate. Preferred salts prepared according to the present invention include the succinate, glutarate and hemisulfate salts.

Those skilled in the art of organic chemistry will appreciate that many organic compounds can form complexes with solvents in which they are reacted or from which they are precipitated or crystallized. These complexes are known as "solvates". For example, a complex with water is known as a "hydrate". Solvates are within the scope of the invention. This invention includes within its scope stoichiometric hydrates as well as compounds containing variable amounts of water.

When used herein, the term "prodrug" means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, Edward B. Roche, ed.; Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987; and in D. Fleisher, S. Ramon and H. Barbra "Improved oral drug delivery: solubility limitations overcome by the use of prodrugs", Advanced Drug Delivery Reviews (1996) 19(2) 115-130, each of which are incorporated herein by reference.

Prodrugs are any covalently bonded carriers that release the compound *in vivo* when such prodrug is administered to a patient. Prodrugs are generally prepared by modifying functional groups in a way such that the modification is cleaved, either by routine manipulation or *in vivo*, yielding the parent compound. Prodrugs include, for example, compounds wherein the amine group is bonded to any group that, when administered to a patient, cleaves to form the amine group. Thus, representative examples of prodrugs include (but are not limited to) acetate, formate and benzoate derivatives of the amine functional group.

When used herein, the term "alkyl" refers to straight and branched groups containing up to six carbon atoms. Examples of such groups include methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tert-butyl, pentyl or hexyl.

When used herein, the term "aryl" refers to, unless otherwise defined, single or fused aromatic rings suitably containing from 4 to 7, preferably 5 or 6, ring atoms in each ring. A fused ring system may include aliphatic rings and need only include one aromatic ring. Examples of suitable aryl rings include phenyl and naphthyl.

When used herein, the term "alkanol" refers to C<sub>1-9</sub>alkyl alcohols, for example methanol, ethanol, industrially methylated spirit (IMS), n-propanol, iso-propanol (IPA), n-

butanol, pentanol, hexanol, heptanol, octanol or nonanol, in particular methanol, ethanol, IMS, IPA or n-butanol.

The invention is illustrated by the following Example.

## 5 EXAMPLE

HPLC was carried out using the following conditions:

Luna 3 $\mu$ m C18 50mm x 2.0mm Reverse Phase Column

10 Solvent A = Water/0.05%TFA

Solvent B = Acetonitrile/0.05%TFA

Gradient profile, 0.00 min = 0% Solvent B; 8.00min = 95% Solvent B

Flow rate = 1.0 ml/min

Temperature = 40°C

15 Injection Volume = 1.0 $\mu$ l

### Example 1

20 DADCP (2,5-diamino-4,6-dichloropyrimidine) (400g, 1.0eq), aminoalcohol.HCl (336g, 1.0eq), sodium bicarbonate (644g, 3.5eq) and n-butanol (3.2L) were heated together at 95-100°C for 8h. The mixture was diluted with n-butanol 6.8L, cooled to 75-80°C and inorganics were removed by filtration. The cake was washed with n-butanol (2 x 600ml).

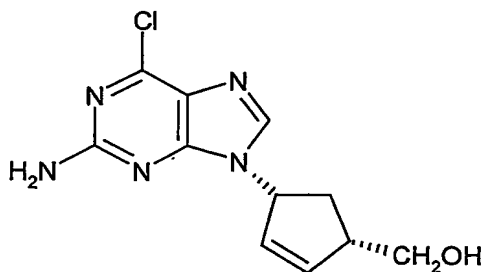
25 The combined filtrate was concentrated down to ca 4L then diluted with n-butanol (2.4L). Triethylorthoformate (368ml, 1.2eq) and catalytic sulfuric acid (4ml, 0.05eq) were added and the mixture was heated at 65-70°C for 6h.

30 Cyclopropylamine (648ml, 4.2eq) was added at about 40-45°C and the mixture was heated at 65-70°C for 5h. The reaction mixture was cooled to 20-25°C then anhydrous sodium carbonate (480g, 2eq) was added and the slurry stirred for 1h. The inorganics were removed by filtration and the cake washed with butanol (2 x 800ml). The filtrate was concentrated to ca 7.5L to remove excess cyclopropylamine then heated to 110-115°C. A solution of glutaric acid (296g) in butanol (2L) was added over 5 mins keeping the temp > 105°C. Cooled to 100-105°C then seeded with authentic abacavir glutarate. The resultant slurry was allowed to cool to 2-5°C over at least 2h, then aged @  
35 2-5°C for 18h. The product was collected by vacuum filtration, the cake washed with cold IPA (3 x 800ml) and dried in-vacuo at 50°C to give abacavir glutarate (82%, purity by HPLC 98.0%a/a). LCMS MH<sup>+</sup> 287, retention time 2.46 min.

40

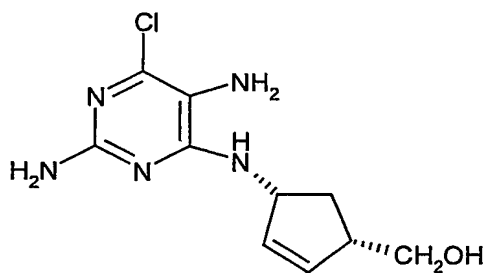
## CLAIMS

1. A process for preparing a chloropurine compound of formula (I)



(I)

or a pharmaceutically acceptable derivative thereof, which comprises ring closure of the compound of formula (VII) or a pharmaceutically acceptable derivative thereof



(VII)

in the presence of catalytic acid and at least one equivalent of a formate derivative.

2. A process according to claim 1 wherein the acid is sulfuric acid, hydrochloric acid, or an alkyl or arylsulfonic acid.

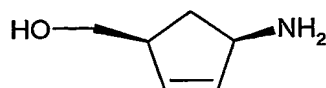
3. A process according to claim 1 or claim 2 wherein the acid is present in an amount of from 0.01 to 0.05 equivalents by mole based on the amount of the compound of formula (VII).

4. A process according to any one of the preceding claims wherein the formate derivative is triethylorthoformate.

5. A process according to any one of the preceding claims wherein the formate derivative is present in an amount of 1 to 1.5 equivalents by mole based on the amount of the compound of formula (VII).

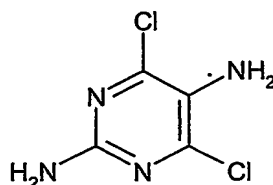
6. A process according to any one of the preceding claims wherein the compound of formula (VII) or a pharmaceutically acceptable derivative thereof is prepared by

condensing an amino alcohol of formula (IV) or a pharmaceutically acceptable derivative thereof



(IV)

with a compound of formula (VIII) or a pharmaceutically acceptable derivative thereof



(VIII)

in the presence of a base.

7. A process according to claim 6 wherein the condensation reaction is carried out in n-butanol in the presence of sodium bicarbonate.

8. A process according to claim 6 wherein the condensation reaction is carried out in n-butanol in the presence of anhydrous potassium carbonate.

9. A process according to any one of the preceding claims wherein the chloropurine compound of formula (I) or pharmaceutically acceptable derivative thereof prepared by the ring closure reaction is converted *in situ* to abacavir or a pharmaceutically acceptable derivative thereof.

10. A process according to any one of the preceding claims substantially as hereinbefore defined with reference to the Example.

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